



# Osimertinib-induced Cardiac Dysfunction in EGFR-Mutated Lung Cancer: A Case Series of Five Patients

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## Abstract

**Introduction:** The gold standard treatment for Epidermal Growth Factor Receptor (EGFR) positive Non-Small Cell Lung Cancer (NSCLC) patients is represented by osimertinib, an irreversible third-generation EGFR inhibitor that has been providing important outcomes' improvements compared to chemotherapy and other target therapies; either upfront or as second line therapy, in case of EGFR T790M detection after previous tyrosine kinase inhibitors (TKI). Osimertinib is generally well tolerated. Most common side effects are diarrhea, rash, paronychia, dry skin and also changes in QT interval.

**Presentation of case series:** Here we report five cases of left ventricular dysfunction during osimertinib treatment, observed between January 2017 and August 2018. The five patients, with a general low cardiovascular risk profile, required a dose modification/discontinuation of the TKI therapy and a specific cardio-protective treatment, normally with a recovery of the systolic function.

**Conclusion:** Both American and European compound labels highlight warnings of cardiomyopathy and changes in cardiac contractility during osimertinib treatment, recommending cardiac monitoring and dose adjustment in patients with cardiac risk factors. In spite of this, a standardized echocardiographic follow-up in the entire population is still not available and recommendations about the use of tissue Doppler echocardiography with more sophisticated indices are missing. With the expanding use of osimertinib we need better strategies to prevent or mitigate cardiovascular damage from cancer therapy in a larger multidisciplinary approach in which every issue is carefully evaluated.

**Keywords:** EGFR; lung cancer, osimertinib; cardiac toxicity; echocardiography

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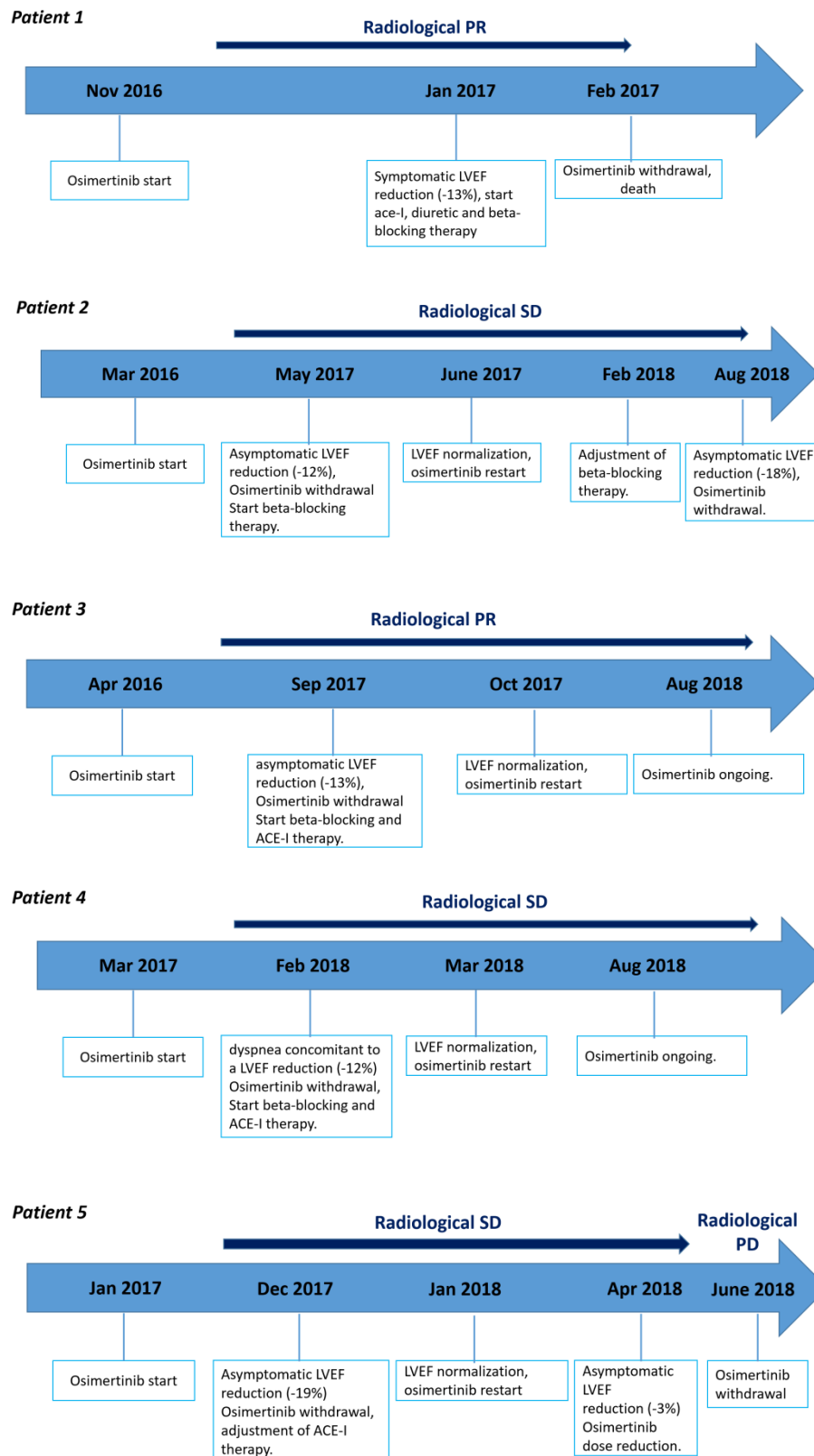
## Introduction

Treatment strategies for advanced NSCLC patients have rapidly evolved in recent years. Tumor molecular profiling led to the identification of genetic alterations, which drive and sustain tumorigenesis. Activating mutations in the EGFR kinase domain are the most known example of oncogenic drivers that can be therapeutically targeted by various small-molecule tyrosine kinase inhibitors (TKIs)[1]. In this patients' setting (10-15% of Caucasian population), TKIs of both first (erlotinib and gefitinib) and second generation (afatinib) demonstrated significant advantages in terms of objective response rate (ORR), progression free survival (PFS) and quality of life (QoL), compared with standard platinum-based doublet chemotherapy [2-4]. Recently, another second generation TKI, dacomitinib, reported a statistically significant and clinically meaningful improvement of overall survival (OS), compared to gefitinib, but limited by more significant side effects[5]. Despite markedly improved outcomes EGFR+ patients eventually experience disease progression, typically within a year from treatment beginning. The most common mechanism of resistance is the acquisition of T790M mutation within the EGFR kinase domain occurring in approximately 60% of cases[6]. Osimertinib, a third-generation EGFR TKI, targets both EGFR activating and T790M resistance mutations. Based on the favorable results from the phase II and phase III AURA trials [7,8], osimertinib received the approval for the treatment of EGFR T790M+ NSCLC who progressed during treatment with prior TKIs. Its efficacy has been also reported in the front-line setting: in the FLAURA study the drug demonstrated a better PFS (18,9 vs 10,2 months) and ORR (80% vs 76%) with a lower toxicity compared to first generation EGFR TKIs[9]. Based on these results it has been approved as a frontline treatment for patients with NSCLC who have tumors harboring EGFR mutations.

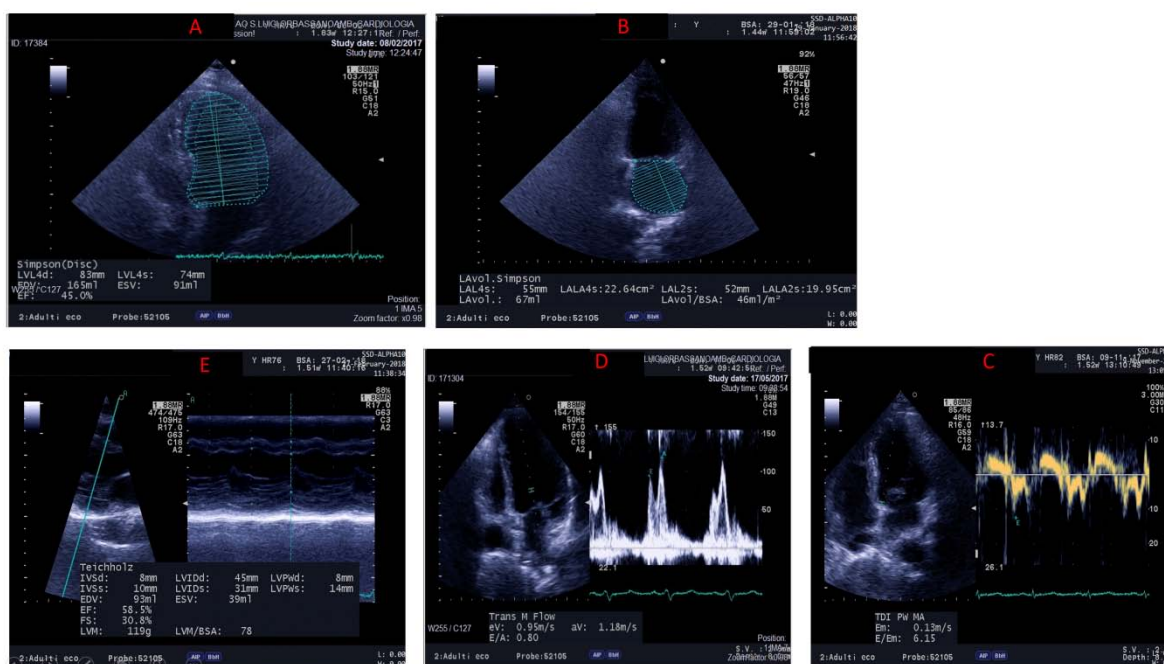
Osimertinib demonstrated a manageable toxicity profile. Most common adverse events (AEs) collected in first and further line trials (almost all grade 1 or 2) were diarrhea, rash, dry skin and paronychia. In the FLAURA study, changes in QT interval (the majority of grade 1 or 2) represented the most common AEs in the cardiac category (29 patients, 10% in the osimertinib group vs 13 patients, 5%, in the standard EGFR-TKI group), and implied treatment discontinuation or dosage reduction in 3% of patients. Other cardiac events, defined as "ejection fraction decrease" occurred in 8 patients (3%) in the osimertinib group and in 3 patients (1%) in the standard EGFR-TKI group and "cardiac failure" respectively in 12 patients (4%) and 6 patients (2%), determining dose interruptions in 1% of patients (14).

Literature data available do not elucidate a clear causal relationship between cardiotoxicity and osimertinib. A consensus about the use of tissue Doppler echocardiography and more sophisticated indices (e.g. global longitudinal strain) for patients without cardiac risk factors is lacking; thus, collaboration between oncologists and cardiologists is strongly recommended. To date, two cases of congestive heart failure have been described only in Asiatic population[10,11].

Here, we report five cases of left ventricular dysfunction associated with osimertinib treatment observed between January 2017 and August 2018 (Figures 1-2).



**Figure1 Patients' clinical timelines:** five cases of left ventricular dysfunction associated with osimertinib treatment



**Figure.2** Main parameters collected during echocardiographic examination. A: left ventricular ejection fraction (EF) B: indexed left atrium end systolic volume indexed (LAVol/BSA). C: E prime wave on tissue Doppler echocardiography. D: E and A wave on trans-mitral pulsed Doppler. E: left ventricular M-mode measures in parasternal long axis view

## Case presentations

### PATIENT 1

A Seventy years-old former smoker men, was diagnosed with advanced stage EGFR-mutated (exon 19 deletion) lung adenocarcinoma in January 2016. He received systemic treatment with gefitinib 250 mg/die with clinical benefit and radiological stable disease (SD) (by RECIST 1.1 Criteria). Due to radiological disease progression and detection of acquired resistance T790M mutation on exon 20 on a tissue biopsy, the patient started osimertinib 80 mg/daily in November 2016 with a RECIST partial response (PR). Any cardiac comorbidity except from arterial hypertension was reported.

In October 2016 a baseline echocardiographic exam showed a normal left ventricle end-diastolic volume indexed on body surface area (LvVol D/BSA: 49 ml/m<sup>2</sup>) and a normal ejection fraction (EF: 60%). Left atrium end-systolic volume indexed on BSA (LAVol/BSA: 29 ml/m<sup>2</sup>) and diastolic function (E/A: 0.7; E/E': 9) were in range. Pulmonary artery pressure (PAPs: 30 mmHg) was normal.

In January 2017, despite a radiological stability of the disease, the patient progressively developed dyspnea. An echocardiographic re-evaluation was performed and revealed a mild EF reduction (45%; -15% from baseline) without left ventricle dilatation, but with a moderate increase of left atrium volume (LAVol/BSA: 47 ml/m<sup>2</sup>). No increase in left ventricle filling pressure was found (E/A: 0.5; E/E': 6) since the patient had already started a diuretic therapy (furosemide 50mg twice daily); PAPs was 35 mmHg. Adequate medical treatment for cardiac failure was prescribed with low dose angiotensin converting enzyme inhibitor (ACEi), ramipril 2.5 mg, bisoprolol 1.25 mg daily and osimertinib was discontinued. Three weeks after drug withdrawal, a new echocardiographic

examination showed a substantial stability in EF (48%). Symptoms and clinical conditions progressively worsened, despite medical treatment and osimertinib withdrawal. To rule out ischemic events, a coronary artery CT scan was performed with the only detection of a critical stenosis of the distal right coronary artery, deputed to supply only a small amount of myocardium. A diagnosis of osimertinib-induced cardiac toxicity was supposed and the heart failure therapy adjusted. Nevertheless, the patient died 10 days later, due to further worsening of cardiac condition.

## PATIENT 2

A Seventy-three years-old never-smoker woman was diagnosed in October 2012 with stage IV, EGFR mutated (exon 19 deletion) NSCLC. After long radiological disease stability with gefitinib 250 mg/die, in March 2016 she developed T790M-induced acquired resistance detected on tissue specimen (together with clinical and radiological lung progression) and started treatment with osimertinib 80mg/daily. The best radiological response during the 2<sup>nd</sup> line treatment was stable disease (SD). The patient reported a cardiologic history of intermittent left bundle branch block and arterial hypertension. The baseline echocardiographic evaluation showed a left ventricle volume at the upper reference limit (LvVol D/BSA: 61 ml/m<sup>2</sup>) with a small increase in indexed left ventricular mass (LVM/BSA: 104 gr/m<sup>2</sup>) and a normal systolic function (EF: 62%). A mild (2+/4) mitral valve insufficiency due to leaflets fibrosis was present. Left atrium volume (LAVol/BSA: 40 ml/m<sup>2</sup>) was enlarged, while the diastolic function (E/A: 0,7; E/E': 7) and the pulmonary artery pressure (PAPs: 30 mmHG) were normal. Along osimertinib treatment, the patient underwent regular echocardiographic controls every three months because of her cardiac history, without any pathological finding.

On May 2017, the routine echocardiography showed a global left ventricular dysfunction (EF 50%, -12% from baseline). The indexed left atrial and left ventricular volumes remained stable. On the contrary, mitral valve insufficiency worsened becoming moderate (3+/4), together with an increase in filling pressure (E/A: 0,7, E/E': 14).

Even though the patient was asymptomatic, osimertinib was suspended for 3 weeks and beta-blocker (bisoprolol 1,25 mg per day) was administered. A new echocardiographic evaluation was performed in June 2017 demonstrating a recovery of left ventricle systolic function (EF: 62%). Thereafter, osimertinib was restarted at the same dosage. Monthly echocardiographic controls showed substantial EF stability (62% → 63% → 58% → 61%) and a progressive diastolic function improvement (E/A: 0,8 → 2,2 → 1 → 0,6; E/E': 18 → 12 → 9 → 7). Due to a new reduction in EF (61% → 54%) and enlargement of left ventricular volume (LvVol D/BSA: 80 ml/mq), without any symptoms, in February 2018 the bisoprolol was up-titrated at 3,75 mg per day and osimertinib suspended. Subsequent echocardiographic controls demonstrated a small EF improvement (58%) with a substantial stability of other parameters. In August 2018 due to a new reduction of EF (40%) osimertinib was temporary suspended. Echocardiographic monitoring is ongoing to evaluate the treatment strategy.

## PATIENT 3

A Forty-seven years-old never-smoker woman was diagnosed in January 2012 with stage IV NSCLC, EGFR mutated (exon 19 deletion). In April 2016 osimertinib 80 mg/daily was undertaken for lung progression to gefitinib 250 mg/die (T790M+ detection on tissue). The best radiological response during the 2<sup>nd</sup> line treatment was PR.

The baseline echocardiographic evaluation did not show any pathological finding. The first echocardiogram, performed six months after osimertinib therapy starts, showed normal dimensions



(LAVol/BSA: 27ml/m<sup>2</sup>; LvVol D/BSA: 54 ml/m<sup>2</sup>) and function (EF: 64%; E/A: 0,8; E/E': 6) of the left cardiac chambers. Two further echocardiograms, performed at nine and twelve months, confirmed these findings. In September 2017, osimertinib was suspended due to asymptomatic LVEF (left ventricular ejection fraction) reduction (EF 51%, -13% from baseline). Left chamber volumes and diastolic function were not affected from this systolic function reduction. Under cardiologic consultation, therapy with bisoprolol (5 mg/day) and perindopril (5 mg/day) was administered, resulting in a partial recovery of cardiac function (EF: 56%, + 5%), and osimertinib restarted (October 2017). Close echocardiographic monitoring continued and the patient underwent a full recovery of the systolic function (EF: 60%).

#### PATIENT 4

A Seventy-one-year-old never-smoker woman was diagnosed in April 2015 with stage IV NSCLC EGFR mutated (exon 19 deletion). Due to lung disease progression to gefitinib 250 mg/day and T790M detection on tissue, the patient started osimertinib 80 mg/daily in March 2017. The best radiological response during the 2<sup>nd</sup> line treatment was SD.

The baseline echocardiographic evaluation showed normal dimensions (LAVol/BSA: 24 ml/m<sup>2</sup>; LvVol D/BSA: 55 ml/m<sup>2</sup>) and function (EF: 58%; E/A: 0,6; E/E': 4) of the left cardiac chambers. Echocardiograms performed in the following eleven months were stable, except for the presence of a mild, stable, circumferential pericardial effusion. In February 2018, osimertinib was suspended due to dyspnea associated with a LVEF reduction (EF 45%, -12% from baseline). Left ventricle and left atrium volumes were both mild dilated (LAVol/BSA: 42 ml/m<sup>2</sup>; LVVol D/BSA: 83 ml/m<sup>2</sup>). The cardiologic consultation led to the introduction of bisoprolol 2,5 mg/daily, furosemide 12,5 mg/daily and perindopril 2,5 mg/daily: a subsequent partial recovery of cardiac function (EF: 54%, + 8%) was observed together with the left chambers volume reduction (LAVol/BSA: 40 ml/m<sup>2</sup>; LVVol D/BSA: 70 ml/m<sup>2</sup>) and regression of dyspnea. Fifteen days after interruption, osimertinib therapy was resumed along with cardiologic therapy prosecution. Clinical and echocardiographic controls showed a stabilization of the cardiac function.

#### PATIENT 5

A Eighty years-old never-smoker woman affected by stage IV EGFR mutated (exon 19 deletion) NSCLC (diagnosis in October 2014) started a first line therapy with gefitinib 250 mg/day; in January 2017 because of lung progression and detection of T790M mutation on plasma, the treatment with osimertinib 80 mg/daily was started. The best radiological response during the 2<sup>nd</sup> line treatment was SD. Arterial hypertension was the only patient's comorbidity. The baseline echocardiographic evaluation did not show any pathological findings. The first echocardiogram performed two months later showed a mild enlargement of the left atrium (LAVol/BSA: 35 ml/m<sup>2</sup>), a mild increase in indexed left ventricular mass (LVM/BSA: 97 gr/m<sup>2</sup>) and normal dimensions (LvVol D/BSA: 61 ml/m<sup>2</sup>) and function (EF: 62%; E/A: 0,5; E/E': 5) of the left ventricle. After eleven months of therapy the patient developed an asymptomatic reduction of the systolic function (EF: 43%, -19% from baseline) and an increase in left ventricle mass and left atrial volume (LVM/BSA: 104 gr/m<sup>2</sup>; LAVol/BSA: 50 ml/m<sup>2</sup>). Osimertinib was temporarily suspended and enalapril therapy titrated from 2,5 mg to 5 mg per day. Three weeks after osimertinib discontinuation, a new echocardiogram showed a systolic function improvement (EF 43% → 55%) and stabilization of left chambers volumes, thus we reintroduced the target therapy. In April 2018 the monthly cardiac follow up demonstrated further reduction in systolic

function (EF 52%). We reduced osimertinib dose at 40mg/die with a stable echocardiographic monitoring until June 2018 when the treatment was permanently discontinued for progressive disease.

## Discussion

American and European osimertinib labels both carry warnings of cardiomyopathy and changes in cardiac contractility during treatment and recommend cardiac monitoring (assessment of LVEF at baseline and during treatment) in patients with cardiac risk factors or with conditions that can affect LVEF. A dose modification/discontinuation is suggested in case of decrease in LVEF of 10% from baseline and below 50%, or in case of symptomatic congestive heart failure [12]. A causal underpinning of relationship between osimertinib and cardiac complications remains weak. Actually, many of the pathways responsible for proliferation in malignant cells also play crucial roles in cardiomyocytes biology, such as survival and electrical and contractile function. Implications of tyrosine kinases in cardiomyocyte survival signaling were first evaluated with trastuzumab (a monoclonal antibody against human epidermal growth factor receptor 2). Another EGFR family member, ERBB1, inhibited by osimertinib, may also be involved in cardio protection and myocyte survival, based on common downstream pathways to the EGFR family receptors [13]. Our case series confirms the potential risk of osimertinib-related cardiac toxicity and allows some hypotheses:

1. Cardiac toxicity seems only partially related to previous cardiac conditions or high cardiovascular profile risk. With the exception of one patient, bearing a moderate valvular disease, none of our patients had previous cardiovascular diseases and their cardiovascular risk profile was low, as in the other two clinical cases already reported [10, 11].
2. Osimertinib cardiac toxicity seems to be more common in female (as in the two previous case reports and in four of our five patients). We can partly explain this observation with the highest prevalence of NSCLC with EGFR mutation in females. However, a gender difference influence could not be excluded [14].
3. Osimertinib cardiotoxicity seems to be reversible and, for this reason, is more likely to be a type 2 cardiotoxicity, like the trastuzumab-related one. Similarly to previous observations made on trastuzumab treated patients, we did not find a worsening of diastolic function, but only a systolic function impairment. Then, type 2 cardiotoxicity could have a different behavior than type 1, in which the systolic function is affected after the development of a diastolic dysfunction [15]. We underline, however, the very small sample size upon which this hypothesis is based.
4. The development of protocols including global longitudinal strain (GLS) and cardiac magnetic resonance is, in our opinion, of paramount importance to identify patients who could benefit of a dosage reduction or a transitory interruption of osimertinib in order to prevent the progression to an overt cardiac dysfunction.
5. The use of beta-blockers and ACEi seems to have a sort of cardio-protective role in patients who develop a reduction of systolic function [16]. This topic needs further investigations in order to determine whether continuing osimertinib in association with a cardioprotective therapy in patients who develop an initial cardiac dysfunction is safe or not.

## Conclusions

In this scenario of paramount efficacy and a global favorable safety profile of osimertinib, a rising awareness of cardiovascular complications can help the minimization of adverse toxicities. A fully understanding of the risk factors plays a critical role. Prospective data investigating the role of routine

high sensitivity troponin evaluation, brain natriuretic peptide (BNP), tissue Doppler and speckle tracking echocardiography could represent tools to early identify cardiac toxicity. With the expanding use of osimertinib, even in front-line setting, we should keep in mind that strategies to prevent or mitigate cardiovascular damage from cancer therapies are important to provide the best care. Cancer treatments are multifaceted and need not only the well-known coordination among oncologists, surgeons and radiation oncologists but also a larger multidisciplinary approach in which every issue, including potential toxic side effects, are carefully evaluated.

## Consent

The patients/families have given their informed consent for the case series to be published.

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